

REMARKS

Applicants request entry of the amendment to claim 6. This amendment was not made sooner because the alleged informality was not pointed out until the final rejection. Applicants request cancellation of claims 8-50 without prejudice and without disclaimer of the subject matter. Applicants note, with appreciation, withdrawal of the previous rejections under 35 U.S.C. §112, first paragraph, relating to enablement and written description.

Claim Amendments and Rejection Under 35 U.S.C. § 112, second paragraph

Claim 6 has been amended to clarify that the polynucleotide comprises the dominant-negative allele of *PMS2* recited in claim 1. This amendment clarifies the relationship of the alleles mentioned in claims 1 and 6 which was said to be confusing. It is respectfully submitted that this amendment clarifies both claims 6 and 7, and the amendment overcomes the rejection.

Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Rejection Under 35 U.S.C. §103(a)

Claims 1-7 are rejected under 35 U.S.C. §103(a) as obvious over Nicolaides *et al.* (1998) *Mol. Cell. Biol.* 18:1635-1641 ("Nicolaides I") or U.S. Patent No. 6,146,894 ("Nicolaides II") in view of PCT Publication No. WO 96/01313 ("Bujard"). The rejection asserts that it would have been obvious to use the inducible expression system of Bujard to express the *PMS2* allele taught by Nicolaides I and II. The Office Action further asserts that one of skill in the art

would have been motivated to use the expression system of Bujard *et al* because it would have provided a (sic) regulated expression of

the dominant negative PMS2 and such would have been desired because continuous expression of the dominant negative PMS2 would have resulted in a high rate of mutation in the genomic DNA of the cell resulting in transformation. It is noted that the dominant negative PMS2 expression was known to cause cancer at the time of the invention.

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To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be a reasonable expectation of success. Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See Manual of Patent Examining Procedure § 2143.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *In re Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998). The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990).

A statement that modifications of the prior art to meet the claimed invention would have been well within the ordinary skill of the art at the time the claimed invention was made because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 U.S.P.Q.2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313, 1318 (Fed. Cir. 2000).

The Patent Office fails to present a *prima facie* case because there is no motivation to combine the primary and secondary references found in the prior art. Instead, the Patent Office uses improper hindsight reconstruction to create the motivation to combine. The Patent Office puts words in the mouths of those of skill in the art (“such would have been desired”) but there is no evidence of those words or suggestions in the prior art itself. The M.P.E.P. cautions that “impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art.” § 2142. The requirement of finding the motivation in the prior art is the safeguard against the improper use of hindsight. That safeguard has been ignored in making the present rejection.

The claims are directed to *in vitro* methods. The products of the methods are cells with new mutations. The cells may be used in culture to create products, *e.g.*, vaccines. The mutant genes in the cells can be isolated and transferred to different cells. The mutant proteins can be harvested from cultured cells. The cells need not be introduced into whole animals. Yet, the alleged motivation is based solely on the possibility that the product cells would be reintroduced into an animal. This alleged motivation is far too

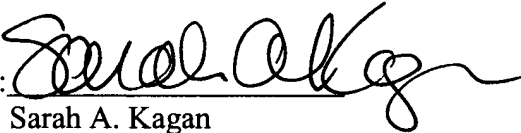
remote from the actual claimed method. It pertains to only one possible use of the product of the claimed method. Moreover, it is a use which is apparently not suggested or taught in the specification.

Without motivation found in the prior art to combine the references, the obviousness rejection fails. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a) over Nicolaides I or II in view of Bujard.

Prompt allowance of the claims is respectfully requested.

Respectfully submitted,

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